Blood Products Advisory Committee Meeting
74th Meeting – September 12, 2002
Silver Spring, MD

Topic: Window period (WP) HIV cases, residual risk and implementation of individual donation nucleic acid testing (ID-NAT)

Issue: Implementation of individual donation NAT for HIV to further reduce window period transmissions from donations screened by pooled sample NAT

Background: Transmission of HIV and HCV by blood and blood products has been dramatically reduced during the past decade as a result of implementation of sensitive and improved tests for viral antibodies and antigens, and, in the case of plasma derivatives, the use of effective virus removal and inactivation methods. The major sources of remaining risk are WP donations, viral variants, atypical seroconversion and laboratory testing error, although most transmissions occurred as a result of WP donations that were not detected by screening assays. Therefore, measures to close the WP were expected to further reduce the low residual risk in HIV and HCV transmission by blood and plasma. In 1994, FDA held a workshop to explore the potential application of nucleic acid based methods to donor screening for HIV. At that meeting, manufacturers and scientific experts indicated that although these methods were clearly sensitive, they were not ready for implementation on a large scale. However, it was felt that development of systems for implementation of nucleic acid methodology for testing blood and plasma donations was a high priority.

In the interim, HIV p24 antigen testing was instituted to reduce virus transmission from window period donations. However, the yield of p24 antigen testing was low and development of NAT was accelerated to further enhance blood safety from HIV transmission. Automation of NAT was critical to high volume screening and rapid turnaround time required in a blood bank setting. It was felt that testing of minipools of plasma donations would be more feasible and a useful interim measure in the implementation of NAT while more fully automated platforms were being developed for testing individual donations. FDA permitted the clinical study of this investigational technology on a large scale. Such large-scale studies were thought to be necessary to demonstrate the efficacy of NAT primarily because the frequency of window period donations is low. Clinical studies to evaluate NAT for whole blood donations were initiated in 1999 under Investigational New Drug Applications (INDs). Data collected under these INDs would be used to support approval of subsequent Biologics License Applications. FDA worked with manufacturers towards validation of NAT assays for donor screening. In addition, manufacturers were provided with validation criteria for replacement of currently licensed HIV p24 antigen tests by pooled and/or individual NAT.

In February 2002, FDA licensed the first pooled and individual sample NAT system for the detection of HIV-1 and HCV RNA in whole blood donations. The assay is performed on pools of 16 or on individual donations. The assay met the current FDA sensitivity standards of 100 copies/ml for the analytical sensitivity of the pool test and 5,000 IU/ml for the original donation. Validation data submitted by the manufacturer supported replacement of currently licensed assays for HIV p24 antigen by both the pooled and individual NAT assay. Other platforms that use pools of 24 donations are also under investigation. In April 2002, FDA issued draft guidance for reporting and labeling requirements for NAT assays and is recommending that blood establishments implement testing by a licensed NAT within six months after publication of the final guidance.

Subsequent to introduction of NAT, three cases of HIV transmission during the window period have occurred. In the first case, a unit of red blood cells from a whole blood donation collected on ---------- that tested negative for HIV by a 24 pool MP-NAT, p24 antigen and antibody assays, transmitted HIV infection to a patient ----------. When the implicated unit was tested later at different dilutions and undiluted by both a licensed and an investigational assay, it was clear that detection was inconsistent at increasing dilutions. Both assays, however, detected the undiluted sample although the test was performed only once. The estimated viral load in the sample was around 150 copies/ml.

In ---------- a similar case of transmission occurred and was discovered in ----------. In this instance the unit was collected from a donor whose blood tested negative by the licensed NAT assay which uses a pool of 16 samples, p24 antigen and antibody assays, and was transfused into two patients, one of whom received fresh frozen plasma and the other, red cells. The HIV status of the donor was recognized at the subsequent donation in ---------. The implicated sample was not available for further testing by NAT. However, CDC, FDA and other labs are performing genotyping analysis to establish linkage between the donor and recipients. The two recipients were identified by lookback which was initiated when the subsequent donation was found to be positive for all markers.

The occurrence of these recent cases of HIV transmission from donated blood despite the implementation of sensitive minipool NAT assays raises the question of whether ID-NAT should be implemented on a large scale in the near future to further reduce the low risk of HIV transmission during the window period. Recent studies indicate that the residual risk of HIV transmission is about 1 in 2 million with pooled sample NAT and approximately 1 in 3 million with ID-NAT and the WP in HIV infection is reduced from 11 days using pooled sample NAT as compared with 7 days using ID-NAT.

In this session, FDA would like to inform the committee of the status of ID-NAT development for future nation-wide implementation. It is FDA's current intention that when feasible and when the appropriate platforms become available, ID-NAT would eventually be implemented for mass screening of donors. The currently licensed platform is semi-automated and requires upgrades including automated sample preparation, reagent preparation etc., to maximize its efficiency for high volume use for

ID-NAT. These upgrades and the necessary regulatory submissions for their approval will require time. Therefore, although ID-NAT may be technically feasible, it may not be operationally so at the present time. This is particularly relevant in a large blood center, where automation capabilities and training of medical technologists and staff will be necessary to ensure component safety and availability. FDA continues to encourage manufactures to facilitate the development of automated platforms for ID-NAT for future large scale implementation. FDA will expedite the review process for approval of related regulatory submissions to ensure timely implementation of ID-NAT for HIV to help further reduce the low risk of transmission from WP donations.